Exhibit II

Suicidality Issues in Clinical Trials: Columbia Suicidal Adverse Event Identification in FDA Safety Analyses

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Division of Metabolism and Endocrinology Products
Advisory Committee Meeting
June 13 2007

Co-Investigators

FDA Classification Work:

Kelly Posner, Ph.D.; Maria Oquendo, M.D.; Madelyn Gould, M.P.H, Ph.D.;Barbara Stanley, Ph.D.; Mark Davies, M.P.H.

C-SSRS Authors:

Posner,K.; Brent,D.; Lucas,C.; Gould, M; Stanley, B; Brown,G.; Zelazny,J.; Fisher,P.; Burke, A; Oquendo,M.; Mann,J.

The Problem...

- Field of medicine challenged by lack of conceptual clarity about suicidal behavior and corresponding lack of well-defined terminology

  -in both research and clinical descriptions of suicidal acts
- Lack of systematic or standardized language used to define suicidal ideation and behavior across clinical trials
- Variability of terms referring to same behaviors, e.g. threat, gesture. Often pejorative and based on incorrect notions about seriousness and lethality in methods

Consequences...

- Difficulty in interpreting the meaning of reported adverse events that occurred in these trials
  - Adverse Events that should have been called suicidal may have been missed
  - Adverse Events may have been inappropriately classified as suicidal

Examples of Difficulties in Adverse Event Labeling

Original Label	Narratives
Personality Disorder	10 y.o. male exhibited sxs of PD of moderate severity and was discontinued, one day later pt. attempted to hang himself w/ a rope after dispute w/ his father. Investigator did not consider this an SAE but rather part of the PD
Accidental Overdose AND Neurosis	The overdose of 6 capsules of study medication was in fact intentional and in response to an argument with the subject's mother.
Medication Error	Age 14: The patient took 11 tablets impulsively and then went to school…the patient denied that it was a suicide attempt.
Hostility	Age 10: Before his mother's call to the site and again after arguing with his stepfather, he wrapped a cord from the miniblinds around his neck, threatening to kill himself.

More Examples of Difficulties in Adverse Event Labeling

Original Label	Narratives
Emotional Lab./ Suicide Attempt	Age 14: The patient is reported to have engaged in an episode of "automutilation" where she slapped herself in the face.
Suicide Attempt	Pt. had thoughts of killing self but had no intention of acting on them
Trauma	"...The patient made an attempt to stab himself in the abdomen on day 49 which resulted in minor injury only. This was not considered a true suicide attempt by the investigator and no action was taken...Hence it was not considered to be clinically significant."
	***** Note severity goes both ways- labels more severe than they should be as well as less severe than warranted***

How to Address this Problem?

- Columbia commissioned by FDA
- A common set of guidelines needed to be applied
- Data needed to be examined consistently
- Developed the research supported Columbia-Classification Algorithm for Suicide Assessment (C-CASA[1])
  - Mandated to be used in all antidepressant and anticonvulsant trials as well as other CNS agents, nonpsychotropic drug classes, including cannabinoid 1 receptor (CB1R) inverse agonists.

[1] Posner et al. American Journal of Psychiatry. 2007;167:1035-1043

How were Suicidal Adverse Events Classified?

Electronic text string search of database for these events

- Search of preferred terms for the following 2 text strings: “suic” or “overdos” “attempt; cut; gas; hang; hung; jump; mutilat; overdos; self damag; self harm; self inflict; self injur; shoot; slash; suic”
- Permitted exclusions for events that represented obvious false positives (e.g., “gas” in “gastrointestinal”)
- All accidental injuries, serious adverse events and deaths

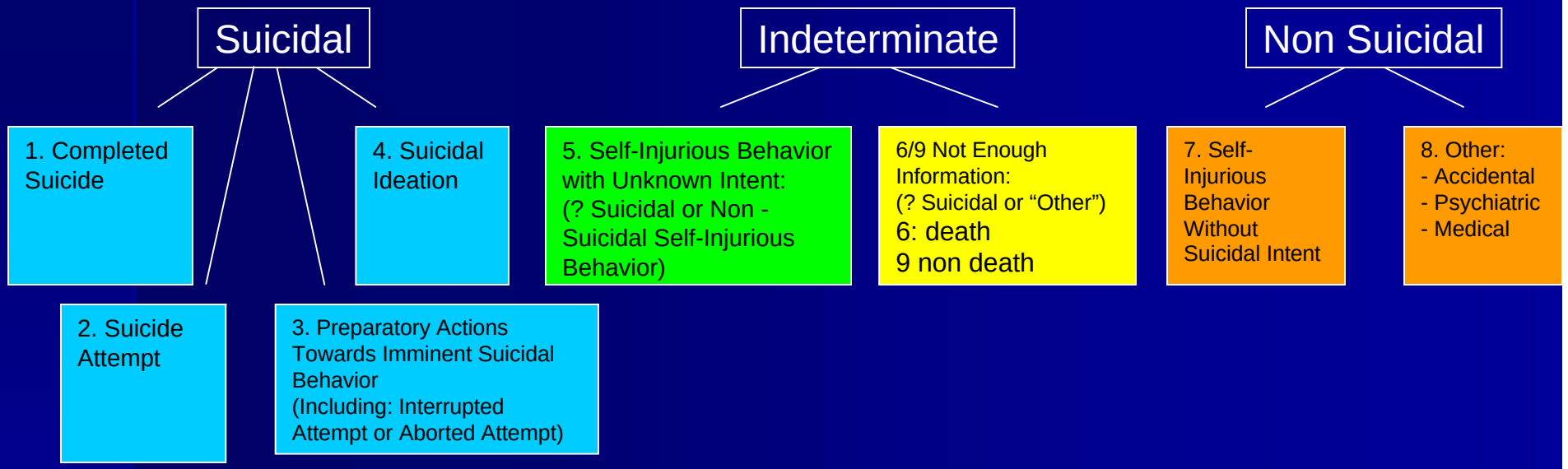
- Companies constructed narratives of events according to FDA/C-CASA guidelines and sent them to the Columbia group.

Blinding of Event Narratives to Avoid Bias

- Received from Company blind to all potential drug identifying information:
  - Drug name
  - Company/sponsor name
  - Patient identification numbers
  - Active or placebo arm
  - *Any and all* medication names and types (e.g. tx with other meds may be associated with a particular antidepressant side effect profile and thus could potentially bias)
  - Primary Diagnosis/Indication of study

- Additional Blinding of potentially biasing information:
  - Original label of event given by investigator or sponsor
  - "serious" or "non-serious" labels

What is the Classification Scheme (C-CASA)?



Columbia- Classification Algorithm for Suicide Assessment: Codes

Suicidal

1. Completed Suicide
2. Suicide Attempt
3. Preparatory Actions Towards Imminent Suicidal Behavior
4. Suicidal Ideation

Indeterminate

5. Self-injurious Behavior Intent Unknown
6. Not Enough Information: Death
9. Not Enough Information: Non-Death

Non Suicidal

7. Self-Injurious Behavior Without Suicidal Intent
8. Other (Accident; Psychiatric; Medical)

Suicide Attempt Definition

- A self-injurious act committed with at least some intent to die, ***as a result of the act.***
- Any non-zero intent to die- does not have to be 100%.
- There does not have to be any injury or harm, just the ***potential*** for injury or harm.
- Intent does not have to be explicit, it can be inferred, from circumstances for example.
- For Example
  - Patient puts gun in mouth and pulls trigger but gun fails to fire
  - Patient wants to die. Ingests some pills as a way to kill self.

Suicidal Ideation Definition

- Thoughts of wanting to die or ending one's life.
- For example:
  - Following a fight with her boyfriend, patient thought about taking an overdose to end her life
  - Patient was feeling depressed and thought his bad luck would never change and wished he were dead

C:CASA Key Findings

- From Previous FDA Safety Analyses (Pediatric Antidepressants)
  - More suicidal events overall, but fewer events were labeled suicidal attempts (50% reduction in attempts)
  - Excellent reliability (median ICC=.86)
  - FDA Audit C-CASA “robust and reproducible” excellent transportability.
  - This FDA safety analysis using C-CASA comprised 1/3 different events than earlier analysis relying on pharmaceutical labels (substantial turnover)

Misclassification can lead to over estimation of risk

- Safety analysis using C-CASA (Hammad et al. 2006) had more precise estimate of risk (tighter confidence interval) compared to a prior analysis relying on an sponsor ratings (Mosholder, 2004).

- This is consistent with previous findings that misclassification leads to overestimation of true risk (Jurek et al. 2005).

Limitations of the Data: *Lessons Learned*

- Studies not designed to assess suicidality
- Association does not mean causality
- Alternative Explanation to Causal Link - Ascertainment Bias
  - Spontaneously generated not systematically elicited
  - Med subjects potentially have more contact with provider consequent to the more common occurrence of physical side effects. (more face-to-face time to hear about suicidal incidents)
  - Possibly accounts for differential rates among subjects receiving drug versus placebo in any safety analysis

Systematic vs. Spontaneous Data: Different Results

- In earlier safety analysis (pediatric antidepressant) a systematically collected data (suicide item from a depression rating scales) did not confirm the risk shown by the adverse event data.
- Thus may be false or misleading results

How to Fix the Problem… Columbia - Suicide Severity Rating Scale

- Systematic administration of a tool designed to track suicidal adverse events across a treatment trial
- ***Prospective version*** of the system we developed for the FDA
- Way to get better safety monitoring and avoid inconclusive results
- This is why FDA is often recommending C-SSRS in ongoing or future studies.

Columbia-Suicide Severity Rating Scale (C-SSRS)

Posner, Brent, Lucas, Gould, Stanley, Brown, Fisher, Zelazny, Burke, Oquendo, & Mann.

- Developed by leading experts/evidence-based
- Feasible, low- burden (typical admin time 5 minutes)
- Assesses *both* behavior and ideation,
- Appropriately assesses and tracks suicidal all events
- Uniquely address the need for a summary measure of suicidality

For all C-SSRS inquiries contact: posnerk@childpsych.columbia.edu

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Lifetime For Baseline or Since Last Assessment	Last Week
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you tried to harm yourself in order to end your life or because you wanted to die/kill yourself?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from…?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) **Indicate if subject has engaged in Non-Suicidal Self-Injurious Behavior :**	**Yes No** ☐ ☐ Total # of attempts _____ ☐	Yes No ☐ ☐ Total # of attempts _____ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?***	**Yes No** ☐ ☐ Total # of interrupted _____	Yes No ☐ ☐ Total # of interrupted _____

Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?***	**Yes** ☐ **No** ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?***	**Yes** ☐ **No** ☐	Yes ☐ No ☐
Absence of Suicidal Behavior: No Suicidal behavior present during the assessment period.	**Yes** ☐ **No** ☐	Yes ☐ No ☐

SUICIDAL IDEATION		
Ask about all 5 types of ideation, starting with least severe (wish to be dead) through most severe.	**Since Last Assessment or For Baseline Time He/She Felt Most Suicidal**	Last Week
Non-suicidal Suicidal ideation present during the assessment period.	**Yes** ☐ **No** ☐	Yes ☐ No ☐
1. Wish to be Dead Subject endorses thoughts about their own death, including any of the following: a wish to be dead/better off dead, wish he/she were never born, thoughts that life is not worth living or the world would be better off without him/her, wish to fall asleep and not wake up, ***Have you wished you were dead or wished you could go to sleep and not wake up?*** ***Do you think that it might be better if you weren't alive any more?*** ***Frequency of Ideation: _____***	**Yes** ☐ **No** ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide *"I've thought about killing myself"* without general thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** ***Frequency of Ideation: _____***	**Yes** ☐ **No** ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when where or how I would actually do it…..and I would never go through with it".* ***Have you been thinking about how you might do this?*** ***Frequency of ideation: _____***	**Yes** ☐ **No** ☐	Yes ☐ No ☐

SUICIDAL IDEATION		
4. Active Suicidal Ideation with Some Intent to Act, Without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** ***Frequency of Ideation: _____***	**Yes** ☐ **No** ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** ***Frequency of Ideation: _____***	**Yes** ☐ **No** ☐	Yes ☐ No ☐

Additional Features Assessed

- Lethality of Attempts
- Other Features of Ideation
  - Frequency
  - Duration
  - Controllability
  - Reasons for Ideation
  - Deterrents

All these items significantly predictive of completed suicide

****Minimum amount of information needed for tracking and severity***.

Various Uses of C-SSRS Within a Study

- Treatment benefit outcomes
- Safety outcomes
- Clinical safety monitoring
- Coordinated efficiently with other measures
- Easily coupled with inclusion/exclusion
  - In past exclusion arbitrary e.g. “serious risk”??
    (criteria can be operationalized and assessed by C-SSRS
    e.g. past attempt ever -early phases; recent attempt-later phase; current ideation (intent or plan))

C-SSRS Current Uses

- 4 years of use in clinical trials
- Large multi-site industry trials nationally and internationally
- Range of therapeutic areas, disorders/indications non-psychotropics, and CNS agents;
  - -Psychiatry
  - -Neurology
  - -Urology
  - -Endocrinology
- Over 20 languages
- NIMH Trials
- Surveillance Efforts
- Community clinics and practice

Conclusions

- Intervention trials using prospective and systematic measurement of suicidality would more clearly delineate the relationship between suicidal adverse events and medication treatment.
- Consistent and systematic assessment (e.g. C-SSRS) can provide more meaningful data within a study, as well as across studies, improving pooled analyses
- Improved assessment of suicidal events is necessary to better inform risk benefit analyses.

Some Perspective on Suicidal Ideation

- Suicidal ideation is a symptom of depressive disorder
- Lifetime prevalence of depressive disorders is 29% (Kessler et al. 2005)
- Estimated 10.5 million people nationally experienced suicidal ideation (1994 CDC Data; Crosby et al. 1999)
- 30,575 Completed Suicides (1994 CDC Data)

Exhibit JJ

FDA Advisory Committee

June 13, 2007

ZIMULTI ® (rimonabant)

sanofi-aventis US

Presentation Agenda

Introduction	**Richard Gural, PhD**
Mechanism of Action	Ken Mackie, MD
Medical Need and Clinical Efficacy	Pierre Rosenzweig, MD
Clinical Safety	Paul Chew, MD
Risk MAP	Richard Gural, PhD
Benefit / Risk	Louis Aronne, MD

Basis for Development in Obesity (1)

- 1996 and 2007 FDA *Draft Guidance for the Clinical Evaluation of Weight-Control Drugs*
  - duration and size of phase 3 studies
    - one year of placebo-controlled exposure in 1500 patients
    - second year of open-label exposure in up to 500 patients
  - efficacy criteria
    - mean weight loss is 5% greater in drug vs. placebo-treated patients OR
    - proportion of patients losing 5% is greater in drug vs. placebo-treated group

Basis for Development in Obesity (2)

- 1996 and 2007 FDA *Draft Guidance for the Clinical Evaluation of Weight-Control Drugs*
  - patient population
    - BMI $\geq$ 30 kg/m^2 OR
    - > 27 kg/m^2 with comorbidities
      - hypertension
      - type 2 diabetes
      - dyslipidemia
- 1998/2000 NIH Clinical Guidelines on Overweight and Obesity
  - since obesity is a chronic disorder, the short-term use of drugs is not helpful

Efficacy Basis for Approval
Phase 3 Studies

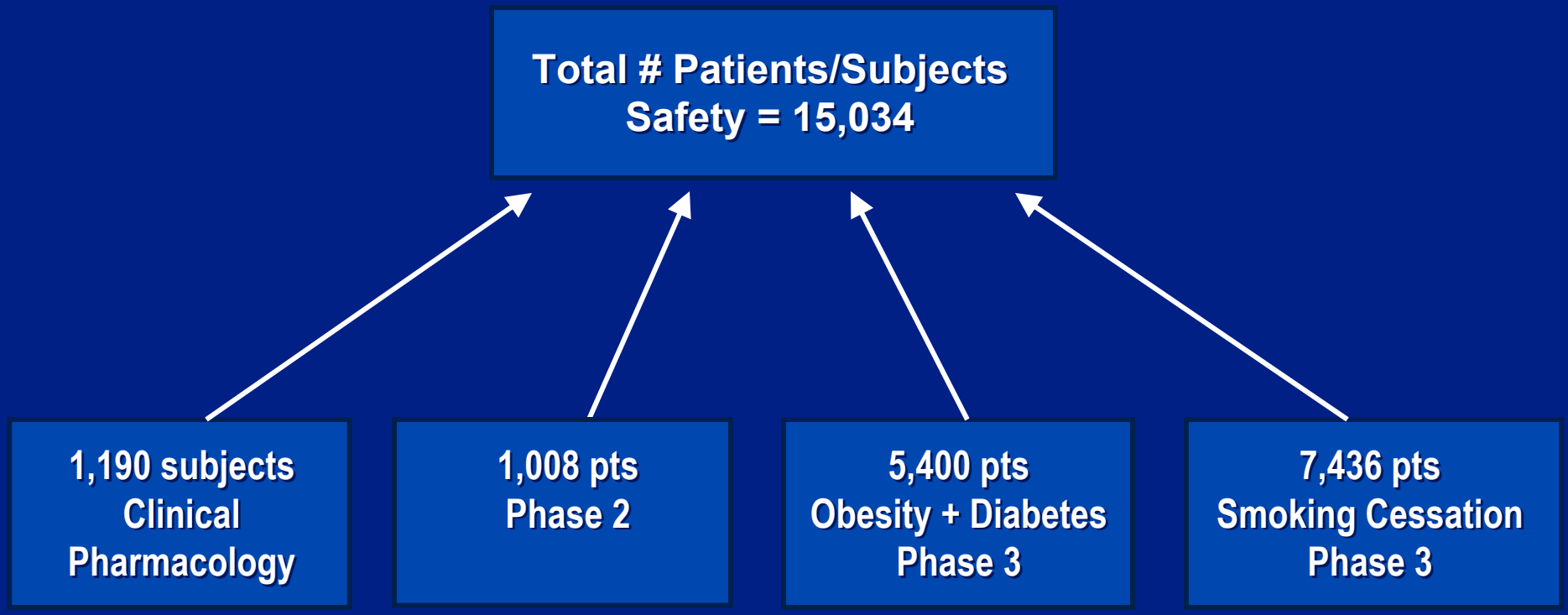
Obesity Program	Treatment Period
RIO-North America*	1 yr + 1 yr
RIO-Europe*	2 years
RIO-Lipids*	1 year
RIO-Diabetes*	1 year

Diabetes Program	Treatment Period
RIO-Diabetes*	1 year
SERENADE*	6 months

* Publication

Rimonabant Safety Population Completed Phase 1 to Phase 3 Studies

- 7,447 patients at 20 mg QD from 1 day to 2 years



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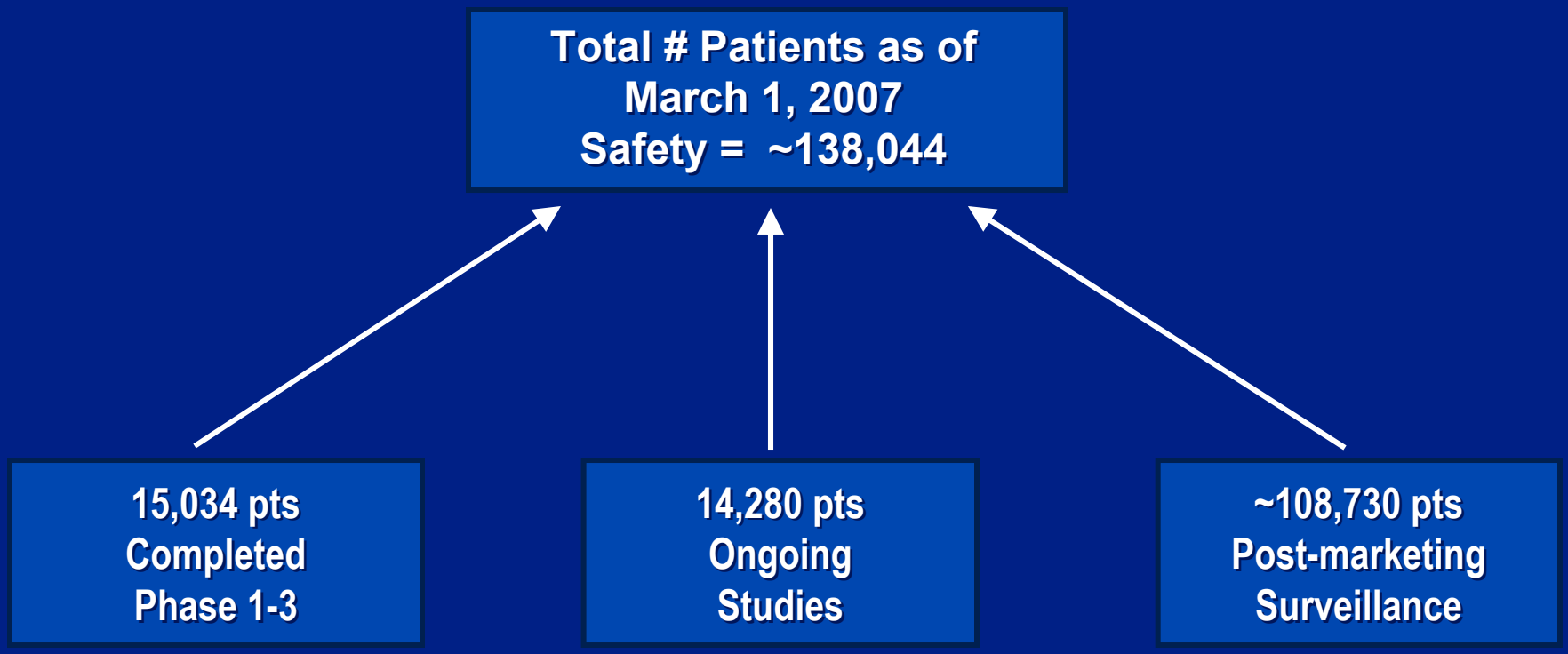
Rimonabant Safety Population



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Ongoing Clinical Development Program

Study Number	Study Title	Number of Subjects Enrolled
EFC5823	ADAGIO-Lipids – treatment of atherogenic dyslipidemia in abdominally obese patients.	799
EFC5826	CRESCENDO – reduction in the risk of major cardiovascular events in abdominally obese patients with clustering risk factors	8269/17000
EFC5827	STRADIVARIUS – inhibition of athersclerosis progression assessed by intravascular ultrasounds in overweight patients with clustering risk factors	838
EFC5828	AUDITOR – inhibition of atherosclerosis progression assessed by carotid artery intima-media thickness in overweight patients with additional risk factors	660
PMC0172	VICTORIA – effect on the amount and the activity of visceral fat in abdominally obese patients with metabolic syndrome	229
EFC5593	ARPEGGIO – effect on glycemic control in type 2 diabetic patients inadequately controlled with insulin	366
EFC5107	RAPSODI – prevention of type 2 diabetes in patients with prediabetic status	2397
EFC6001	RIO ASIA – weight-reducing effect and safety in obese patients with or without comorbidities	642
	TOTAL	**14200**

ZIMULTI® (rimonabant)

- Selective and neutral antagonist of the cannabinoid-1 (CB_1) receptor
- Tablet
- 20 mg once daily

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Rimonabant Pharmacokinetics

- Metabolized by CYP3A and amidohydrolases
  - potent inhibitors of CYP3A increase rimonabant exposure up to 2.7 fold
- Terminal half-life 16 days
  - steady state accumulation of 3.3 fold in 25 days
- No effect of rimonabant on CYP enzymes

Global Regulatory Status

- Approved in 37 countries and marketed in 18
- Marketing Application submitted in EU – April 2005
- Approved via Centralized Procedure – June 2006
- Approved EU Indication:
  - an adjunct to diet and exercise for the treatment of obese patients (BMI $\geq$ 30 kg/m^2), or overweight patients (BMI > 27 kg/m^2) with associated risk factor(s), such as type 2 diabetes or dyslipidemia
- EU Risk Management Plan (EU-RMP)
  - initial version – June 2006

US Regulatory History

- NDA 21-888 (obesity + type 2 diabetes) submitted April 2005; approvable letter – February 2006
- Complete response submitted October 2006
  - response included:
    - updated safety data for completed and ongoing studies
    - review of all neurological and psychiatric events
    - proposed risk management plan
- Agreed to 3 month extension for review – February 2007
- Submitted SERENADE study in T2D – February 2007
- Advisory Committee Meeting – June13, 2007
- PDUFA Action Letter Date – July 26, 2007

Proposed Indications

as an adjunct to diet and exercise for the treatment of overweight patients with BMI > 27 kg/m^2 and at least one other cardiovascular risk factor, or for the treatment of obese patients with a BMI ≥ 30 kg/m^2.

in combination with metformin or a sulfonylurea to improve glycemic control and reduce weight in patients with type 2 diabetes and a BMI > 27 kg/m^2 when diet and exercise plus a single agent do not result in adequate control.

Who is the Appropriate Patient?

- NOT Everyone
- Appropriate
  - patients with a BMI > 27 kg/m^2 with at least one cardiovascular risk factor or a BMI ≥ 30 kg/m^2
  - chronic indication intended for long-term use
- Not Appropriate
  - past history of depressive disorders and/or suicidality or patients with a diagnosis of depressive disorders or current anti-depressant therapy
  - treatment with anti-epileptic therapy

Consultants

Mechanism of Action

Ken Mackie, MD – Indiana University

Endocrinology

Louis Aronne, MD – Medical College of Cornell University

George Bray, MD – Pennington Biomedical Research Ctr

Michael Jensen, MD – Mayo Clinic

Donna Ryan, MD – Pennington Biomedical Research Ctr

Internal Medicine

Patrick Moriarty, MD – University of Kansas Medical Center

Consultants

Psychiatry

Robert Anthenelli, MD – University of Cincinnati College of Medicine

Bassalingappa Hungund, PhD – New York State Psychiatric Institute

Ranga Krishnan – Duke University Hospital

J. John Mann, MD – New York State Psychiatric Institute

Consultants

Neurology

Walter Bradley, MD – University of Miami

Richard Mattson, MD – Yale University

Dan Mikol, M.D., PhD – University of Michigan Medical Center

Maral Mouradian, MD – Robert Wood Johnston University Hospital

Epidemiology

Judith Jones, M.D., PhD – The Degge Group

Biostatistics

Gary Koch, PhD – University of North Carolina

Exhibit KK

Clinical Safety

Dr. Paul Chew

Metabolism, Diabetes, Thrombosis
Clinical Development

Overall Clinical Safety

- **Overall Clinical Development Program**
- Overall Safety Profile & Serious Adverse Events
- Adverse Events of Interest
- Safety Conclusion

Overall Clinical Development Program Completed Studies

- A total of 15,034 patients were exposed to at least one dose of rimonabant (5 or 20 mg QD):
  - 40 Phase 1 studies (1190 subjects)
  - 6 Phase 2 studies (1008 patients)
  - 13 Phase 3 studies (12,836 patients)
    - 7447 with 20 mg exposure (1 day to 2 years)
  - In total, 6665 pt-years exposure (3478 pt-years to 20 mg)

Safety Analysis: Completed Phase 3 Studies

- Analysis followed ICH* guidelines for safety data pooling, using version 9.0 of the MedDRA dictionary:
  - Obesity pool of 7 studies (RIO-NA, RIO-EU, RIO-LIPIDS, RIO-DIABETES, EFC5031, EFC5745, ACT3801)
  - Type 2 Diabetes pool of 2 studies (RIO-DIABETES [also in Obesity pool] and SERENADE)
  - Smoking Cessation pool of 5 studies (4 STRATUS, CIRRUS)
  - Combined pool of obesity & smoking cessation programs for 12 studies (4 RIOs, EFC5031, EFC5745, ACT3801, 4 STRATUS, CIRRUS)
- Discussion today on obesity and type 2 diabetes and other populations when appropriate

* Conference on Harmonization (ICH) M4E 'Common Technical Document (CTD) for the Registration of Pharmaceuticals for Human Use'

Number of Patients Exposed in Completed Phase 3 Studies (1)

Studies	Placebo	Rimonabant	
		5 mg	20 mg
Obesity			
RIO-Europe	305	603	599
RIO-North America	1233	1214	1219
RIO lipids	342	345	346
RIO-diabetes	348	358	339
ACT3801 (Binge eater)	146	-	143
REBA	80	-	76
EFC5745	20	-	20
TOTAL obesity	**2474**	**2520**	**2742**
Type 2 diabetes			
SERENADE	140	-	138
*RIO-Diabetes**	*348*	*358*	*339*
TOTAL diabetes	**488**	**358**	**477**

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Number of Patients Exposed in Completed Phase 3 Studies (2)

Studies	Placebo	Rimonabant	
		5 mg	20 mg
Smoking cessation			
STRATUS-US	261	262	261
STRATUS-EU	260	256	267
STRATUS-META	268		262
STRATUS-WW	664	2351	3023
CIRRUS	-		754
TOTAL Smoking	**1453**	**2869**	**4567**
TOTAL obesity + smoking cessation + type 2 diabetes	**4067**	**5389**	**7447**

Ongoing Clinical Studies

- 11 ongoing clinical studies* as of March 1, 2007
- Blinded treatment 1:1 randomization rimonabant to placebo
- 14,280 patients exposed in clinical trials* (overall 7855 patient-years, of which 3927 patient-years are in rimonabant 20 mg group)

* Phase 1 (PDY5352, PDY6632, POP10059) and Phase 3 (EFC5107, EFC5827, EFC5828, EF5826, EFC6001, EFC5593, EFC5823, PMC_0172)

Overall Clinical Safety

- Overall Clinical Development Program
- **Overall Safety Profile & Serious Adverse Events**
- Adverse Events of Interest
- Safety Conclusion

Obesity Program: General Safety Profile (AEs in ≥ 2%* of Rimonabant-treated Patients)

%	Placebo N=2474	Rimonabant 20 mg N=2742
Any Event	**81.4**	**86.3**
Gastrointestinal disorders		
Nausea	4.7	13.6
Diarrhea	5.8	7.7
Vomiting	2.3	4.7
Nervous system disorders		
Dizziness	4.1	7.3
Psychiatric disorders		
Anxiety	2.1	5.9
Insomnia	3.4	5.8
Mood alterations with depressive symptoms	2.8	4.7
Depressive disorders	1.7	3.9
Others		
Influenza	9.1	10.3
Asthenia / fatigue	4.4	6.1
Gastroenteritis	3.5	4.5
Contusion	1.1	3.1
Hot flush	0.8	2.0

* And ≥ 1% over placebo, Obesity program: 4 RIOs, EFC5031, EFC5745, ACT3801

MM-95

Type 2 Diabetes Program: General Safety Profile (AEs in ≥ 2%* of Rimonabant-treated Patients)

%	Placebo N=488	Rimonabant 20 mg N=477
Any event	**73.2**	**80.7**
Gastrointestinal disorders		
Nausea	5.5	11.3
Diarrhea	5.9	7.1
Vomiting	1.8	5.5
Nervous system disorders		
Dizziness	4.3	9.6
Paresthesia	0.8	2.9
Psychiatric disorders		
Anxiety	2.9	5.2
Insomnia	2.0	4.6
Mood alterations with depressive symptoms	2.7	6.1
Depressive disorders	1.4	2.5
Others		
Asthenia / fatigue	3.9	7.1
Arthralgia	4.5	5.7
Hypoglycemia	1.4	4.0
Muscle spasms	0.6	2.7

* Note: and ≥ 1% over placebo

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Summary: General Safety Profile of Rimonabant

- In the obesity program, AEs reported in ≥ 2 % of patients were:
  - gastro-intestinal disorders (nausea/vomiting)
  - neurological disorders (dizziness)
  - psychiatric disorders (anxiety, insomnia, mood alterations, depressive disorders)
  - general disorders (asthenia/fatigue)
- In type 2 diabetes program, additional AEs included hypoglycemia, paresthesias and muscle spasms

Obesity Program: Fatal Cases (Completed Studies)

	Placebo	Rimonabant	
		5 mg	20 mg
Cause of Death	**N=2474**	**N=2520**	**N=2742**
Deaths n (%)	**3 (0.12)**	**3 (0.12)**	**4 (0.15)**
Cardiac arrest	-	1	-
Cardiac failure	-	-	1
Coronary artery disease	-	-	1
Road traffic accident	-	-	1
Completed suicide	-	1	-
Uterine cancer	-	-	1
Septic shock	-	1	-
Pulmonary embolism	1	-	-
Cerebral hematoma /CVA	1	-	-
Cerebral hemorrhage	1	-	-

Obesity program: 4 RIOs, EFC5031, EFC5745, ACT3801

Overall Clinical Safety

- Overall Clinical Development Program
- Overall Safety Profile & Serious Adverse Events
- **Adverse Events of Interest**
- Safety Conclusion

Adverse Events of Interest

- Psychiatric disorders
  - depression-related events
  - suicidality-related events
  - anxiety disorders
- Neurological adverse events
  - overall
  - multiple sclerosis
  - seizures

Depressive-Related Events in Obesity Phase 3 Studies – Specific Methodology

- Prospective monitoring in RIO studies
  - to facilitate psychiatric consultation in a non psychiatric environment
  - to increase the sensitivity of detection of depressive events through regular patient self assessment scale (HAD)
- Retrospective assessment through a specific questionnaire
  - focus on outcome and associated symptoms including suicide attempt/ideation

MM-101

Obesity Program: Depressive-Related Events

%	Placebo N=2474	Rimonabant 20 mg N=2742
Depressed mood disorders and disturbances	**4.5**	**8.4**
Mood alterations with depressive symptoms	2.8	4.7
Depressive disorders	**1.7**	**3.9**

Obesity program: 4 RIO, EFC5031, EFC5745, ACT3801

MM-102

Obesity Program: Main Characteristics of Depressed Mood Disorders and Disturbances

	Mood Alterations with Depressive Symptoms		Depressive Disorders	
	Placebo N=70	Rimonabant 20 mg N=129	Placebo N=43	Rimonabant 20 mg N=106
Past history of depressive disorders	16%	14%	40%	42%
Treatment discontinuation	26%	26%	58%	61%
Corrective therapy (CT)	35%	29%	72%	72%
Time to recovery + CT (median)	119	91	73	131
Time to recovery – CT (median)	42	50	103	30
Hospitalization (n)	0	0	1	4

Obesity program: 4 RIOs, EFC5031, EFC5745, ACT3801

MM-103

Impact of Past History of Depressive Disorders

N (%)	No Past History of Depressive Disorders		Past History	
	Placebo N=2282	Rimonabant 20 mg N=2507	Placebo N=192	Rimonabant 20 mg N=235
Any Psychiatric Event	**248 (10.9)**	**584 (23.3)**	**55 (28.6)**	**108 (46.0%)**
Mood alterations with depressive symptoms	59 (2.6)	110 (4.4)	11 (5.7)	19 (8.1)
Depressive disorders	**26 (1.1)**	**61 (2.4)**	**17 (8.9)**	**45 (19.1)**
Anxiety	44 (1.9)	132 (5.3)	7 (3.6)	29 (12.3)
Insomnia	70 (3.1)	139 (5.5)	13 (6.8)	20 (8.5)

Obesity program: 4 RIO, EFC5031, EFC5745, ACT3801

MM-104

Depression-Related Events: Summary

- Two different types of events:
  - mood alterations
    - less need for corrective treatment
  - depressive disorders
    - more frequent corrective treatment
    - hospitalizations (1 placebo, 4 rimonabant)
- Depressive disorders more frequently reported with rimonabant 20 mg compared to placebo (3.9% vs 1.7%)
- Main predictor was a past history of depression; (2.4% vs. 1.1%) if no past history

MM-105

Suicidality-Related Events Methods of Analysis

- In agreement with FDA, the sponsor followed C-CASA: Columbia-Classification of Adult Suicidality Assessment validated algorithm* to search for suicide-related events in completed double-blind, randomized studies
- Blinded narratives of adverse events from 22 studies sent for assessment by C-CASA:
  - removed information on patients, study name, study drug, dates and chronology
  - Phase 2 (9 studies) & completed Phase 3 (13 studies) studies

* FDA Psychopharmacologic Drugs Advisory Committee and the Pediatric Advisory Committee, September 13, 2004

Categorization of "Suicidality" C-CASA

Independent and blind categorization by experts as follows:

1: Completed suicide

2: Suicide attempt

3: Preparatory acts toward imminent suicide behavior

4: Suicidal ideation

5: Self-injurious behavior, intent unknown

6: Not enough information (fatal)

7: Self-injurious behavior, no suicidal intent

8: Other: accident, psychiatric, medical

9: Not enough information (non fatal)

Suicidality Assessment per C-CASA in All Indications

All completed Phase 2 and 3 Studies* as of March 2007

N (%)	Placebo (N=3411)	Rimonabant 5 mg (N=5254)	Rimonabant 20 mg (N=7851)
Definitely suicidal behavior/ideation			
(Categories 1 to 4)	21 (0.62)	11 (0.21)	48 (0.61)
Possibly suicidal			
(Categories 5, 6, 9)	2 (0.06)	1 (0.02)	5 (0.06)

- Total = 88 cases under placebo or rimonabant

* Phase 2 studies: obese, smoking, alcohol, schizophrenia, and Phase 3 studies: RIO, REBA, SERENADE, EFC5745, ACT3801 and Smoking

MM-108

Suicidality Assessment per C-CASA in Obesity and Diabetes

All completed Phase 2 and 3 Studies* as of March 2007

Category ** N (%)	Placebo (N=2214)	Rimonabant 5 mg (N=2720)	Rimonabant 20 mg (N=3081)
Definitely suicidal behavior/ideation	***8 (0.36)***	***8 (0.29)***	***20 (0.65)***
2 Suicide attempt	0 (0)	0 (0)	1 (0.01)
4 Suicidal ideation	8 (0.36)	8 (0.29)	19 (0.62)
Possibly suicidal	***1 (0.05)***	***1 (0.04)***	***2 (0.06)***
6 Not enough information (fatal)	0 (0)	1 (0.04)	0 (0)
9 Not enough information (non fatal)	1 (0.05)	0 (0)	2 (0.06)

* DRI3388, PDY3796, DRI5747, EFC4733, EFC4735,EFC4736, EFC4743, ACT3801, EFC5031, EFC5745, EFC5825, ACT4389, EFC4474, EFC4964, EFC4796, EFC5794, DRI3388, ACT4855, EFC4798, Ph1 studies as a single strata, Run-in periods in RIO studies

**Category including at least one event

MM-109

Odds Ratio for Suicidality (95%)

Method	FDA	Sponsor
Overall	**1.9 (1.1, 3.1)**	**1.3 (0.8, 2.3)**
Smoker	3.9 (1.2, 16.8)	1.0 (0.2, 4.9)
Other*	1.4 (0.4, 4.4) 0.97 (0.2, 5.7)	1.1 (0.4, 2.8)
Obesity and diabetes	1.8 (0.8, 3.8)	1.6 (0.7, 3.5)

*for schizophrenia and alcohol study

MM-110

Investigator-Reported Suicides

	Completed Trials
Investigator Reported Suicides	1 (5 mg)
Patient-Years	6979
Events/100K Patient Years (95% CI)	14 [0.0, 80]

As of May 2007: two reported cases of suicide in ongoing clinical trials and one post-market case of suicide reported (28 May 2007) via second-hand information in a patient allegedly receiving rimonabant.

BMI > 30 = 13 per 100,000 pt-years: Mukamal, et al. Body Mass Index and Risk of Suicide Among Men. *Arch Intern Med* 2007; 167:468-475.

Completed Suicide in Ongoing Studies

Study Sex Gender TT group	Exposure on rimonabant	Past History	Clinical Description	Stressors
STRADIVARIUS Male 36 yrs 20mg *received:* *Aug 2006*	10 months	Myocardial infarction 1week prior to inclusion	About 8 months after starting study drug, patient with no psychiatric history presented a non-serious mild depressive mood., irritability and fatigue. Serious professional and financial stressors. Depression worsened within 3months.No corrective treatment. No psychiatrist or specialist consulted	Financial problems, overworked
CRESCENDO Male 77 yrs 20mg *received:* *22 May 2007*	45 weeks	Depression at age of 40. additional further episodes	About 10 months after study start, the patient became depressed. He discontinued rimonabant on his own. He visited a psychiatrist who prescribed SSRI and committed suicide 1 week later. Psychiatrist evaluation revealed depression and loss of energy/interest and no associated suicidal ideation.	Marital difficulties Physical handicap due to worsening of neuropathy

MM-112

Completed Suicide in Completed Study

Study Sex Gender TT group	Suicidal Behavior (Date of Onset)	Past History	Description	Stressors
RIO NA Male 63 yrs 5mg *received: March 2002*	Gunshot wound (D157) "Apparent suicide" according to investigator	Depressive symptoms Anxiety	"At last visit: no sign of despondency, hopelessness, or outwards sign the patient was suicidal" From nurse: can't eat, slept 30 hours Was found dead, in front of his house."	Past involvement in a federal witness protection program, Pending court decision

MM-113

Patients with Suicidal Behavior/Ideation SAEs** Assessed per C-CASA in Ongoing Phase 3b Studies*

Category N (%)	Placebo (N~7980)	Rimonabant 20 mg (N~7980)
Definitely suicidal behavior/ideation	***11 (0.14)***	***24 (0.30)***
1 Completed suicide	0 (0.0)	2 (0.03)
2 Suicide attempt	2 (0.03)	0 (0.0)
4 Suicidal ideation	9 (0.11)	22 (0.28)

- Total = 35 cases under placebo or rimonabant

* Phase 3 studies: EFC5107, EFC5827, EFC5828, EF5826, EFC6001, EFC5593, EFC5823, PMC_0172 and EFC5749

** Includes relevant SAE data through 29 May 2007

MM-114

Suicidality Summary
Obesity and Diabetes Studies

- An imbalance was seen in obesity and diabetes studies for “definitely suicidal behavior/ideation”.
  - (0.65%) vs. (0.36%)
- Suicidal ideation was always associated with depression or adjustment disorders
- A causal link has not been established between suicidality and the use of rimonabant

Obesity Program: Frequency of Anxiety Symptoms and Panic Disorders

%	Placebo N=2474	Rimonabant 20 mg N=2742
Anxiety symptoms	**3.8**	**9.0**
Anxiety	2.1	5.9
Stress	1.5	1.6
Nervousness	0.3	1.2
Agitation	< 0.1	0.4
Tension	0	< 0.1
Panic disorders	**< 0.1**	**0.8**
Panic attack	< 0.1	0.7
Panic disorder	0	<0.1
Panic reaction	0	<0.1

Obesity program: 4 RIOs, EFC5031, EFC5745, ACT3801

MM-116

Obesity Program: Main Characteristics of Anxiety Disorders and Symptoms

	Placebo N=2474	Rimonabant 20 mg N=2742
Anxiety Disorders and Symptoms	N=100	N=278
Past history	9%	7.9%
Treatment discontinuations	14%	19.8%
Corrective therapy	48%	41%
Time to recovery + CT (median)	65	43
Time to recovery – CT (median)	45	35
Resulting in hospitalization (n)	0	1

Obesity program: 4 RIOs, EFC5031, EFC5745, ACT3801

Obesity Program: Most Frequent Neurological Adverse Events

%	Placebo N=2474	Rimonabant 20 mg N=2742
Any event	**12.5**	**20.2**
Sensory changes	**9.3**	**14.8**
Dizziness	4.1	7.3
Paresthesia/Hypoesthesia	1.7	2.8
Sciatica	0.6	1.2
Motor impairment	**2.3**	**3.4**
Tremor	<0.1	0.9
Cognitive difficulties	**2.1**	**4.1**
Memory loss	0.7	1.5

Obesity program: 4 RIO, EFC5031, EFC5745, ACT3801

MM-118

Obesity Program: Neurological Adverse Events Leading To Discontinuation > 0.1%

	Placebo N=2474	Rimonabant 20 mg N=2742
Any Event %	**16 (0.6)**	**61 (2.2)**
Sensory changes	**8 (0.3)**	**38 (1.4)**
Dizziness / Vertigo	3 (0.1)	21 (0.8)
Paresthesia/Hypoesthesia	1 (<0.1)	12 (0.4)
Motor Impairments	**5 (0.2)**	**11 (0.6)**
Tremor	0 (0)	5 (0.2)
Cognitive Difficulties	**3 (0.1)**	**18 (0.7)**
Memory loss	2 (<0.1)	6 (0.2)

Obesity program: 4 RIO, EFC5031, EFC5745, ACT3801

MM-119

Confirmed New Occurrences of Multiple Sclerosis (MS)

Reported MS	Completed Trials	Ongoing Trials*
Placebo (n)	1	0
Patient-Years	3451	3927
Events/100K Patient Years (95% CI)	29 (1, 161)	0 (0, 97)
Rimonabant 5 mg (n)	2	NA
Rimonabant 20 mg (n)	0	0
Patient-Years (5 mg and 20 mg)	6979	3927
Events/100K Patient Years (95% CI)	29 (3, 103)	0 (0, 97)

* As of March 1, 2007

** As of end-April 2007 (post-marketing): No case reports of confirmed multiple sclerosis, 1 case of bilateral papillitis [optic neuritis] 1 month after starting rimonabant reported as potential MS

Incidence rate of MS in the general population is 7.5 per 100,000 person-years (Mayr et al, 2003)

MM-120

Multiple Sclerosis in Completed Studies

- Suspected MS (20 mg)
  - 49 year old woman evaluated for balance disorder; MRI scan not consistent with MS. Updated information 3.5 years after end of study reveals no new events and normal yearly evaluations.
- Pre-existing MS with relapse (20 mg)
  - 42 year old woman with MS diagnosed almost 5 years prior to entering the study. Relapse on treatment similar to relapses prior to and after study.

Seizure Evaluation

- Exclusion Criteria in Phase 3 Studies
  - patients with treated epilepsy
  - 72 patients with a seizure history were randomized in Phase 3.
- Methodology
  - adverse events from the HLGT* MedDRA (9.0) "seizures (incl subtypes)" up to 75 days post-dosing in all studies
  - string search** to for potential cases (completed & on-going trials)
  - independent, blind review by neurology experts with questions to investigators for additional information
    - classification of cases as "possible or likely", or "unlikely"

* HLGT: High Level Group Term

** *"convuls", "petit mal", "grand mal", "epilep", "tonic clonic","focal", "partial", "generaliz", "absence", "conscious", seizur, "ictus", "ictal", "clon"*

MM-122

Seizures in Completed Studies: FDA and Sponsors Analysis

- FDA analysis
  (Table 31 of FDA BP)
  - included only studies (n=8) with a report of seizure
  - excluded cases in placebo run-in phase (2 cases) and > 3 months after study end (1 placebo case).
  - included cases in non-placebo controlled phases or studies (2 cases in 20 mg).
  - compared rimonabant 20mg versus placebo.
- Sponsor analyses
  - included all completed studies (Phase 1, 2 ,3) with/without events.
  - included all reported seizures whatever the phase.
  - compared rimonabant all doses versus placebo.
  - 2 Analyses performed:
    - all seizure cases (unlikely, likely or possible)
    - likely or possible seizures as assessed by external experts

MM-123

Incidence Rate of Seizures in Completed Studies

- 19 cases were reviewed by the experts:
- 14 were assessed as likely or possible seizures
- 5 were assessed as unlikely seizures

Number of events / Extent of exposure in patient-years [a] (%)				Relative Risk (90% confidence interval) Rimonabant vs Placebo
	Rimonabant			
Placebo (3451)	5 mg (3263)	20 mg (3597)	All doses * (6979)	
Analysis of the 19 cases in the completed studies				
8 (0.23%)	2 (0.06%)	9 (0.25%)	11 (0.16%)	0.68 (0.31, 1.51)
Analysis of the 14 cases assessed as "likely/possible seizures" by the experts				
6 (0.17%)	2 (0.06%)	6 (0.17%)	8 (0.11%)	0.66 (0.27, 1.68)

(a) Patient exposure includes placebo run-in periods and non controlled study periods

Unstratified analysis including placebo run-in

* Only doses for which there is at least one event are shown.

MM-124

Incidence Rate (Patient-Years) of Seizures in Completed Studies

FDA Analysis : 8 studies, 20 mg versus Placebo
Excludes 2 placebo run-in cases and one late event.
Includes two 20 mg cases in non-placebo controlled studies.

Placebo	20mg	RR 20 mg vs. placebo (95% CI)
5/2811	9/3527	1.69 (0.56, 5.63)

Sponsor analysis: all studies, all cases (unlikely, possible, likely)
Includes all reported cases

Placebo (a)	20mg	All doses	RR 20 mg vs. placebo (90% CI)	RR All doses vs. placebo (90% CI)
8/3451	9/3597	11/6979	1.08 (0.48,2.47)	0.68 (0.31, 1.51)

(a) Patient exposure includes placebo run-in periods and non controlled study periods

MM-125

Seizures – Ongoing Studies

- 8 cases of possible seizures have been reported
- All were blindly adjudicated by the same experts and then unblinded
  - possible / likely: 20 mg (4) and placebo (2)
  - unlikely: 20 mg (2)
- Estimated incidence in patient-years, in 20 mg:
  - 6/3927 (0.15%) for all reported cases
  - 4/3927 (0.10%) for 'possible/likely' cases

  Similar to that observed in completed studies (0.25%)

MM-126

Overall Clinical Safety

- Overall Clinical Development Program
- Overall Safety Profile & Serious Adverse Events
- Adverse Events of Interest
- **Safety Conclusion**

Overall Safety Conclusion (1)

- Rimonabant is well-tolerated in the proposed patient populations with a defined safety profile
- **Depression**
  - reported more with rimonabant (3.9% vs. 1.7%)
  - past history of depression predicts recurrent depression for both placebo and rimonabant
- **Suicidality**
  - imbalance in suicidal ideation
  - always associated with treatable depression or adjustment disorders

MM-128

Overall Safety Conclusion (2)

- **Overall Neurological Adverse Events**
  - most frequent AEs: dizziness, paresthesia/hypoesthesia, tremor, memory loss
  - no imbalance in serious neurological events
- **Seizures**
  - no increased seizure rate with rimonabant
  - treated epileptic patients excluded from Phase 3 completed studies
  - caution in patients being treated for epilepsy
  - treated epileptic patients are included in ongoing studies

Overall Safety Conclusion: Safety Perspective (3)

- Sibutramine Package Insert (weight loss)
  - *"**Psychiatric**: Cases of depression, suicidal ideation, and suicide have been reported rarely on patients treated with sibutramine. However, the relationship has not been established between the occurrence of depression and/or suicidal ideation and the use of sibutramine. If depression occurs during treatment with sibutramine, further evaluation may be necessary."*

Overall Safety Conclusion (4)

- Ongoing worldwide post-marketing experience and risk-management program has shown no new safety signals

Exhibit LL

ZIMULTI

SANOFI-AVENTIS

NDA 21-888

Endocrinologic and Metabolic Drugs Advisory Committee Meeting
Silver Spring, Maryland
June 13, 2007

Amy G. Egan, M.D., M.P.H.
Division of Metabolism and Endocrine Products

Center for Drug Evaluation and Research

Outline

- Efficacy findings and conclusions for the indication of weight management
- Safety concerns
  - Neurological adverse events
  - Seizures
  - Psychiatric adverse events
  - Suicidality

FDA Guidance Criteria for Efficacy of Weight-Management Drugs

1. The drug's effect is significantly greater than that of placebo with the mean drug-associated weight loss exceeding mean placebo weight loss by at least 5%.
2. The proportion of subjects who reach and maintain a loss of at least 5% of their initial body weight is significantly greater in subjects on drug than in those on placebo.

Efficacy Conclusions

- Rimonabant 20 mg daily along with a hypocaloric diet was shown to reduce body weight by approximately 5% relative to hypocaloric diet plus placebo
- Rimonabant-associated weight loss was accompanied by improvement in levels of triglycerides, HDL-C, and HbA_{1c} in subjects with type 2 DM

Efficacy Conclusions (cont'd)

- Relative to placebo, rimonabant had no effect on levels of total cholesterol or LDL-C
- For unclear reasons, reductions in systolic and diastolic blood pressure were less than expected given the degree of weight loss

Caveats

- High attrition
  - Year 1 drop out rates: ~ 32% to 49%
  - Year 2 drop out rates: ~ 23% to 58%
  - No systematic follow-up of dropouts
- Last observation carried forward (LOCF) was used in this study as the 1° analytic method
- Generalizability
  - Middle-aged Caucasian females
  - Greater efficacy in Caucasian vs. African-American and younger vs. older
  - Subjects with a history of significant depression excluded

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Rimonabant Database

As of 18 December 2006, the cumulative database for rimonabant consists of:

- 1308 healthy subjects from 37 completed Phase 1 studies
- 1230 patients from 5 completed Phase 2 studies
- 13,644 patients from 13 completed Phase 3 studies
  - 6761 obese patients in 8 weight management/ diabetes studies
  - 6883 patients in 5 smoking cessation studies)

Exposure to Rimonabant

- Subject exposure to rimonabant 20 mg indications as of December 18, 2006:
  - 0 to < 6 months: 2256 subjects
  - 6 to <12 months: 1619 subjects
  - 12 to < 18 months: 592 subjects
  - 18 to 24 months: 441 subjects

Selection of Events of Interest

- Datasets:
  - Adverse event dataset
  - Associated psychiatric symptoms dataset
  - Controlled substance dataset
- Studies with re-randomization:
  - Same treatment during the entire study

Statistical Methodology

- Meta-analysis stratified by study
- Included 14 randomized phase 2 and 3 trials
- Per study sample sizes ranged from 20 to 3,000 per group
- Study durations ranged from 4 to 104 weeks
- Primary treatment comparison: rimonabant 20 mg vs. placebo

Statistical Methodology

- RR, OR, RD
- Safety outcomes with relatively rare events (seizure, suicidality): an exact meta-analysis and a fixed-effects meta-analysis were used
- Safety outcomes with more common events (neurological AEs and psychiatric AEs): Fixed and random effects meta-analyses were used
- Primary analysis used first randomization data only
- Sensitivity analyses were performed using second randomizations

Neurological Adverse Events

Endocannabinoids and the Nervous System

- CB_1 receptors abundant in the cerebellum, cortex, hippocampus, hypothalamus, and basal ganglia (involved in memory, motor function and reward behaviors)
- CB_1 receptors also present on the peripheral nerves
- Neuroprotection of CNS and PNS

Neurological Adverse Events

- Occurred in 27.4% of rimonabant 20 mg treated subjects vs. 24.4% of placebo treated subjects
- Responsible for 3.5% of discontinuations in the rimonabant 20 mg treated subjects vs. 1.3% of placebo treated subjects

Sensory Changes

PREFERRED TERM	RIMONABANT 20 MG N=2176 N (%)	PLACEBO N=1602 N (%)
Total	**306 (14.1)**	**151 (9.4)**
Dizziness	186 (8.5)	89 (5.6)
Paresthesia	37 (1.7)	17 (1.1)
Hypoaesthesia	31 (1.4)	14 (0.9)
Vision blurred	16 (0.74)	8 (0.5)
Dysgeusia	6 (0.28)	3 (0.19)
Dizziness postural	5 (0.23)	3 (0.19)
Facial hypoaesthesia	5 (0.23)	0
Dysaesthesia	3 (0.14)	2 (0.12)
Burning sensation	2 (0.09)	1 (0.06)
Oral hypoaesthesia	2 (0.09)	1 (0.06)
Anosmia	2 (0.09)	1 (0.06)
Hypogeusia	2 (0.09)	1 (0.06)
Parosmia	1 (0.05)	2 (0.12)
Visual acuity reduced	1 (0.05)	2 (0.12)
Ageusia	1 (0.05)	1 (0.06)
Photopsia	1 (0.05)	1 (0.06)
Scintillating scotoma	1 (0.05)	0
Blindness (incl transient)	1 (0.05)	0
Amaurosis (incl fugax)	1 (0.05)	0
Altered visual depth perception	1 (0.05)	0
Dizziness, exertional	1 (0.05)	0
Diplopia	0	2 ().12)
Neuritis	0	1 (0.06)
Formication	0	1 (0.06)
Meralgia paresthetica	0	1 (0.06)

Motor Impairment

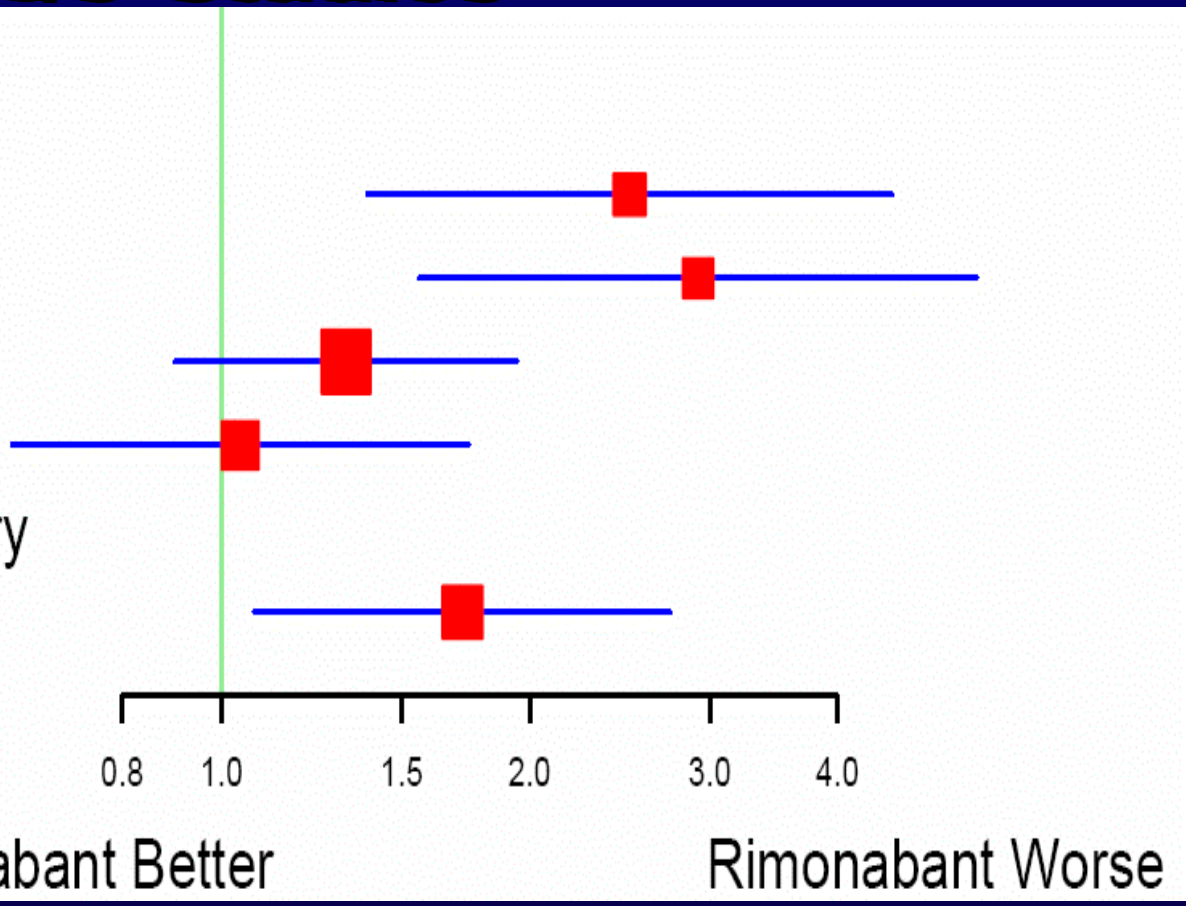
PREFERRED TERM	RIMONABANT 20 MG N=2176 N (%)	PLACEBO N=1602 N (%)
Per Sanofi SAP		
Total	**36 (1.7)**	**8 (0.5)**
Tremor	21 (1.0)	0
Dysphonia	3 (0.14)	2 (0.12)
Facial palsy	3 (0.14)	1 (0.06)
TIA	2 (0.09)	2 (0.12)
Dysarthria	2 (0.09)	0
Speech disorder	1 (0.05)	1 (0.06)
Aphonia	1 (0.05)	0
Hemiparesis	1 (0.05)	0
Supranuclear palsy	1 (0.05)	0
Ischemic stroke	1 (0.05)	0
Cerebral hemorrhage	0	1 (0.06)
Cerebral ischemia	0	1 (0.06)
Additional per FDA		
Total	**31 (1.4)**	**12 (0.75)**
Carpal tunnel syndrome	13 (0.6)	8 (0.5)
Balance disorder	7 (0.3)	1 (0.06)
Restless legs syndrome	4 (0.18)	0
Hyporeflexia	2 (0.09)	1 (0.06)
Motor dysfunction	2 (0.09)	0
Clonus	1 (0.05)	0
Clumsiness	1 (0.05)	0
Tinel's sign	1 (0.05)	0
Coordination abnormal	0	1 (0.06)
Hyperreflexia	0	1 (0.06)

Cognitive Disorders

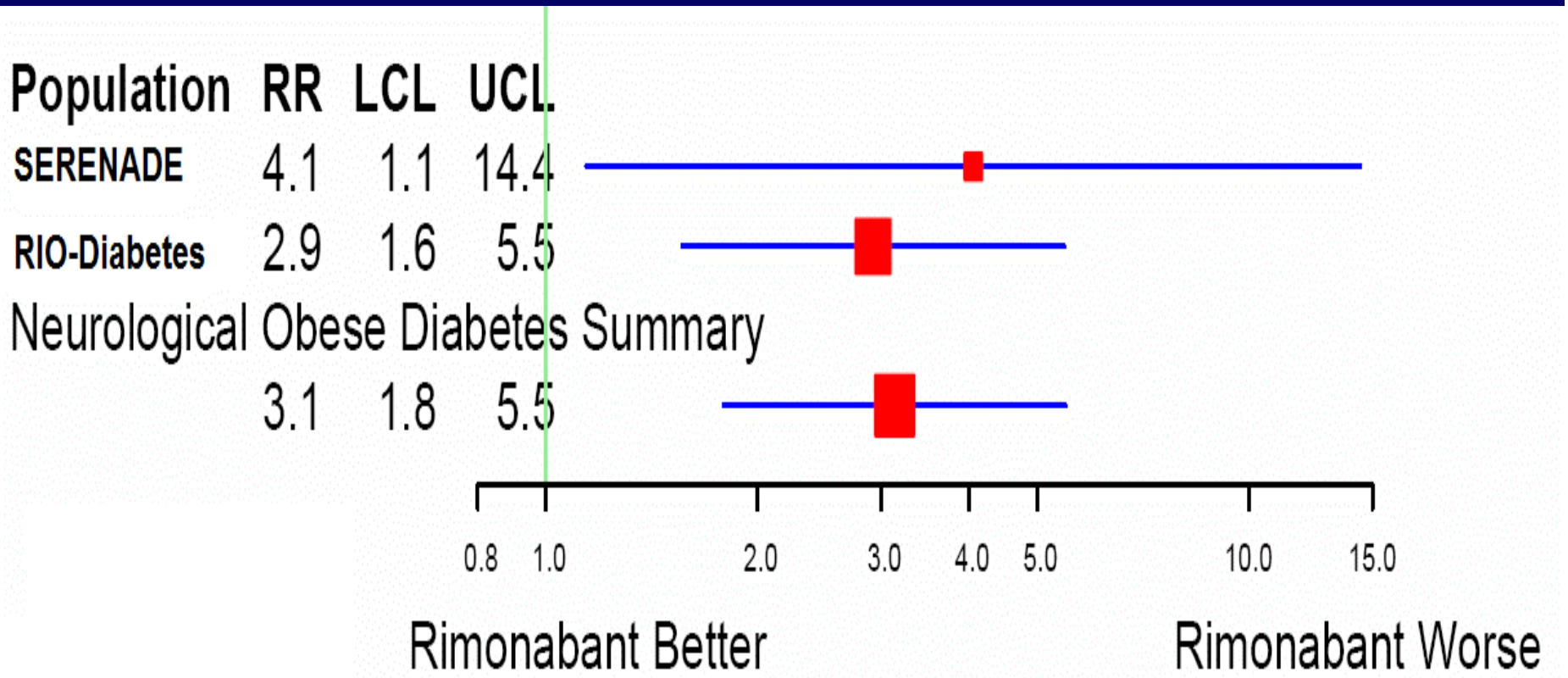
PREFERRED TERM	RIMONABANT 20 MG N=2176 N (%)	PLACEBO N=1602 N (%)
Total	**117 (5.4)**	**53 (3.3)**
Amnesia	16 (0.74)	8 (0.5)
Memory impairment	16 (0.74)	7 (0.44)
Disturbance in attention	15 (0.69)	10 (0.62)
Syncope vasovagal	12 (0.55)	7 (0.44)
Lethargy	12 (0.55)	5 (0.31)
Syncope	10 (0.46)	6 (0.37)
Somnolence	10 (0.46)	5 (0.31)
Disorientation	9 (0.41)	0
Confusional state	6 (0.28)	0
Cognitive disorder	5 (0.23)	0
Spacey feeling	3 (0.14)	
Memory loss	2 (0.09)	1 (0.06)
Mental impairment	1 (0.05)	0
Depressed level of consciousness	0	2 (0.12)
Loss of consciousness	0	1 (0.06)
Sedation	0	1 (0.06)

Relative Risk for Neurological Adverse Events RIO Studies

Study	RR	LCL	UCL
RIO Lipids	2.5	1.39	4.5
RIO Diabetes	2.9	1.56	5.5
RIO N.A.	1.3	0.90	1.9
RIO Europe	1.0	0.62	1.7
Neurological (RIO) Summary	1.7	1.1	2.7



Relative Risk for Neurological Adverse Events Diabetes Studies



Multiple Sclerosis

- Clinical trials data: Cannabinoids can reduce the spasms, spasticity, or tremor of MS
- Pre-clinical data: Mouse models of MS suggest that CB receptor activation may oppose the progression of MS
  - Slows neurodegenerative process
  - Reduces inflammation
  - Promotes remyelination

Multiple Sclerosis

- Numbers small to date
  - RIO
    - 2 confirmed MS cases on Rim 5 mg
    - 1 un-confirmed MS case on placebo
  - Smoking cessation
    - 2 suspected cases on Rim 20 mg
  - Post-marketing
    - 1 case of optic neuritis; MRI suggestive of MS
    - 1 case in subject with MS with exacerbation on Rim
- Lag time to diagnosis
- Initial vague symptomatology
- Theoretic possibility
- Biologically plausible

Seizures

Endocannabinoids and Seizure Potential

- Endocannabinoid system has been implicated in regulating seizure duration and frequency.
- Seizure activity elicits an increase in endocannabinoids which activate pre-synaptic CB_1 receptors with subsequent regulation of neuronal hyperexcitability and seizure termination

Pre-Clinical Data Supporting Seizure Risk

- 6% of rats and mice and 20% of monkeys developed seizures while receiving long-term treatment with doses of rimonabant 0.5-2 times the 20 mg dose versus 1.5% of control mice and no control rats or monkeys
- Rimonabant accumulates 2-fold in the brain with multiple dosing

Exclusion Criteria Relevant to the Evaluation of Seizure

- Presence of any clinically significant neurological disease
- Presence of treated epilepsy
- Prolonged administration (> 1 week) of neuroleptics within 3 months prior to screening visit
- Subjects discontinued from the trials if treated with a neuroleptic

Cases of Seizure

INDICATION	ORIGINAL NDA			UPDATED NDA		
	Rim 20 mg	Rim 5 mg	Placebo	Rim 20 mg	Rim 5 mg	Placebo
Total	4	2	1	9	2	5
Obesity	4	2	1	7	2	1
Smoking	-	-	-	2	0	1
Schizophrenia	-	-	-	0	0	2
Alcoholism	-	-	-	0	0	1

Relative Risk for All Reported Seizures

	Rim 20 mg	Rim 5 mg	Placebo	RR (CI)
All studies	9/3527.3 (0.255%)	2/3204.8 (0.062%)	5/2811.2 (0.178%)	1.43 (0.48, 4.72)
Obesity Studies	7/2608 (0.268%)	2/2438.7 (0.082%)	1/2259.3 (0.044%)	6.06 (0.94, 137.71)

Seizures in Ongoing Studies

- 8 cases of seizure in ongoing studies
  - 6 on rimonabant 20 mg
  - 2 on placebo
- Ongoing studies all have a 1:1 randomization

Seizure Conclusions

- Biological plausibility linking rimonabant to seizure risk
- Pre-clinical data indicate proconvulsant effect of rimonabant
- Exclusion criteria screened out high-risk individuals from clinical trials
- Although the current clinical data perhaps suggest an increased seizure risk with rimonabant, only clinical experience will clarify this potential risk

Psychiatric Adverse Events

Endocannabinoids and Psychiatric Disorders

- Endocannabinoids act as modulators in pathological conditions
  - Anxiety, phobia, depression, post-traumatic stress disorder
- CB_1 receptors are abundant in the pre-frontal cortex
  - Regulation of mood, aggression and/or impulsivity and decision making
- CSF levels of the endogenous cannabinoid anandamide correlate inversely with psychotic symptoms in schizophrenic patients

Exclusion Criteria Relevant to the Evaluation of Psychiatric Adverse Events

- Presence of any clinically significant psychiatric disease
- History of severe depression defined as:
  - Depression necessitating hospitalization or;
  - History of 2 or more recurrent episodes of depression or;
  - History of suicide attempt or;
  - Prolonged administration (more than 1 week) of anti-depressants within 3 months prior to screening
- Subjects discontinued from the trials if started on an anti-depressant
- 11,225 subjects were screened for RIO; 113 (1%) failed screening due to these exclusion criteria

Baseline History of Depressed Mood Disorders and Disturbances

Study	Rimonabant 20 mg	Rimonabant 5 mg	Placebo
Pooled	**179/2503 7%**	**201/2520 8%**	**95/1602 6%**
RIO Europe	33/599 5.5%	24/603 4.0%	10/305 3.3%
RIO Lipids	20/346 5.8%	30/345 8.7%	12/342 3.5%
RIO Diabetes	13/339 3.8%	17/358 4.7%	24/348 6.9%
RIO North America	113/1219 9.3%	130/1214 10.7%	49/607 8.1%

- Ongoing at randomization: 1.4% on rimonabant 20 mg vs. 1.1% on placebo

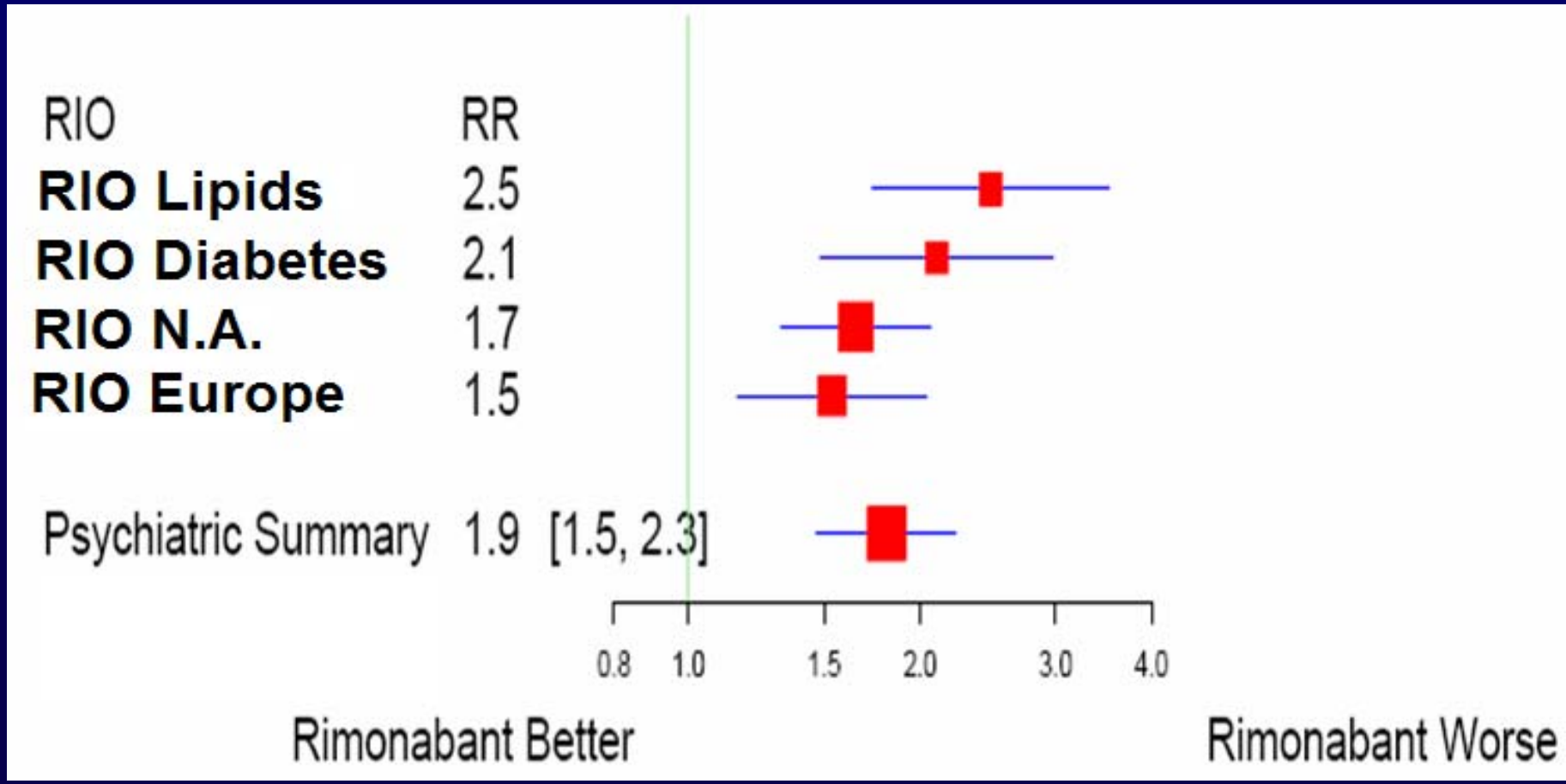
Psychiatric Adverse Event Terms

- Primary System Organ Class (SOC): Psychiatric Disorders
  - High Level Group Terms (HLGT)
    - » Preferred Terms (PT)
  - Anxiety Disorders and Symptoms
    - » (anxiety, nervousness, stress, tension)
  - Depressed Mood Disorders and Disturbances
    - » (depression, depressed mood, anhedonia, dysthymic disorder)
  - Sleep Disorders and Disturbances
    - » (insomnia, parasomnia, somnolence)
  - Mood Disorders and Disturbances
    - » (affect alteration, crying, mood altered)

Psychiatric Adverse Event Rates by High Level Group Term (RIO)

High Level Group Term	Rimonabant 20 mg (N=2176) N (%)	Placebo (N=1602) N (%)
Pooled	569 (26)	225 (14)
Anxiety Disorders and Symptoms	233 (11)	79 (5)
Depressed Mood Disorders and Disturbances	196 (9)	83 (5)
Sleep Disorders and Disturbances	170 (8)	67 (4)
Mood Disorders and Disturbances	60 (3)	12 (0.8)

Relative Risk of Psychiatric AE (RIO)



Relative Risk of Psychiatric Adverse Event by Subgroups

- Age
  - 65 years or older RR = 3.1
  - Less than 65 years RR =1.7
- Geographic location
  - US studies RR = 1.7
  - Non-US studies RR = 1.8

Relative Risk of Psychiatric Adverse Event – by Subgroups

- Gender
  - Males RR = 2.1
  - Females RR = 1.7
- 5% Weight-Loss Response
  - Responders RR = 1.9
  - Non-responders RR=1.9

Psychiatric Adverse Event by Baseline History of Depressed Mood (RIO)

	SUBJECTS WITH A BASELINE HISTORY OF DEPRESSION	
	Yes N=475	No N=6150
Subjects with ≥ 1 Psychiatric Adverse Event (%)	153 (32.2)	1082 (17.6)

- 1082/1235 (88%) of subjects who experienced a psychiatric adverse event did not have a baseline history of Depressed Mood Disorders and Disturbances

Treatment of Psychiatric Adverse Events

	Rimonbant 20 mg	Placebo
Discontinuation	8.5%	3%
Anxiolytic or hypnotic	8.5%	4.1%
Anti-depressant	4.8%	2.9%

Psychiatric Adverse Events Conclusions

- Rimonabant 20 mg was associated with an ~ 2-fold increase in the risk of psychiatric adverse events
  - Anxiety disorders and symptoms
  - Depressed mood disorders and disturbances
  - Sleep disorders and disturbances

Suicidality

Columbia Suicidality Categories

Category	
1	Completed suicide
2	Suicide attempt
3	Preparatory acts toward imminent suicide behavior
4	Suicidal ideation
5	Self-injurious behavior, intent unknown
6	Not enough information (fatal)
9	Not enough information (non-fatal)

Suicidality Assessment

- 1201 patient narratives assessed by the Posner group
- 91 suicidality cases identified:
  - Definitely (Columbia categories 1, 2, 3, or 4)
  - Possibly (Columbia categories 5, 6, or 9)
- Majority of cases were assessed suicidal ideation (Columbia Category 4):
  - Placebo: 14
  - Rim 5 mg: 10
  - Rim 20 mg: 40

Statistical methodology

- 13 studies used in the analysis
- RIO North America and EFC4796 re-randomized patients
  - First randomization used in primary analysis
  - EFC4796 used the Rim 5 mg group as the control group (no placebo group in first randomization)
  - Sensitivity analyses performed for the 2nd randomization

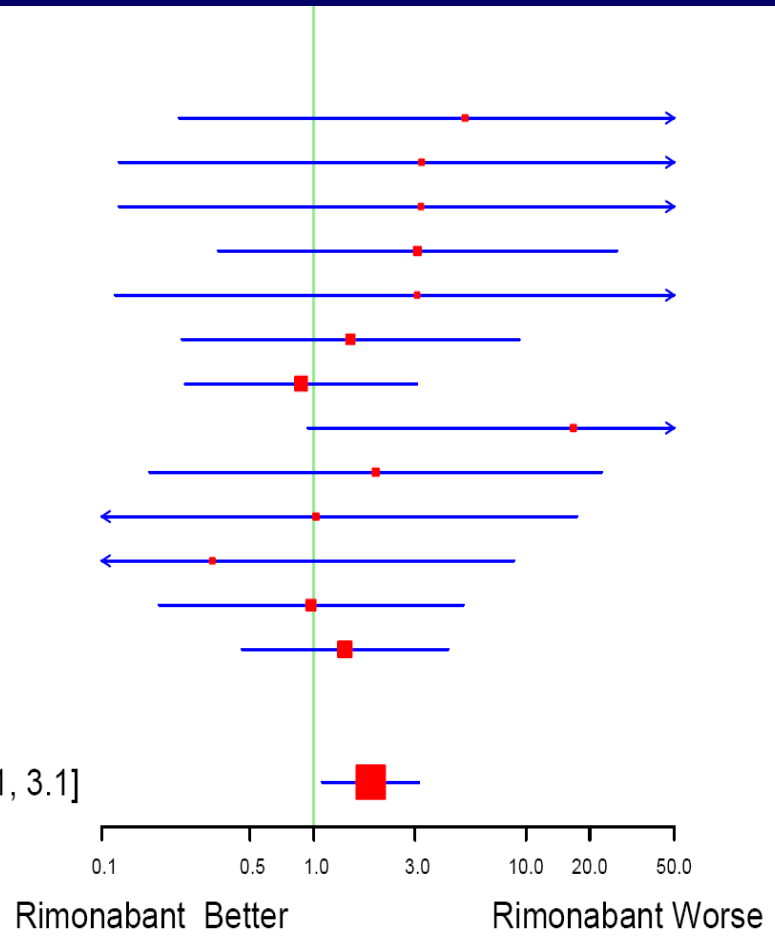
Suicidality Cases in the Analyses

- Total number of suicidality cases contributing to the analyses is 74

C-CASA Classification	Placebo (n=2909)	5 mg (n=5121)	20 mg (n=6802)
1 Complete suicide			
2 Suicide attempt	7		4
3 Preparatory acts toward imminent suicide		1	
4 Suicidal ideation	13	6	39
5 Self-injurious behavior, intent unknown			
6 Not enough information (fatal)		1	
9 Not enough information (non-fatal)			3

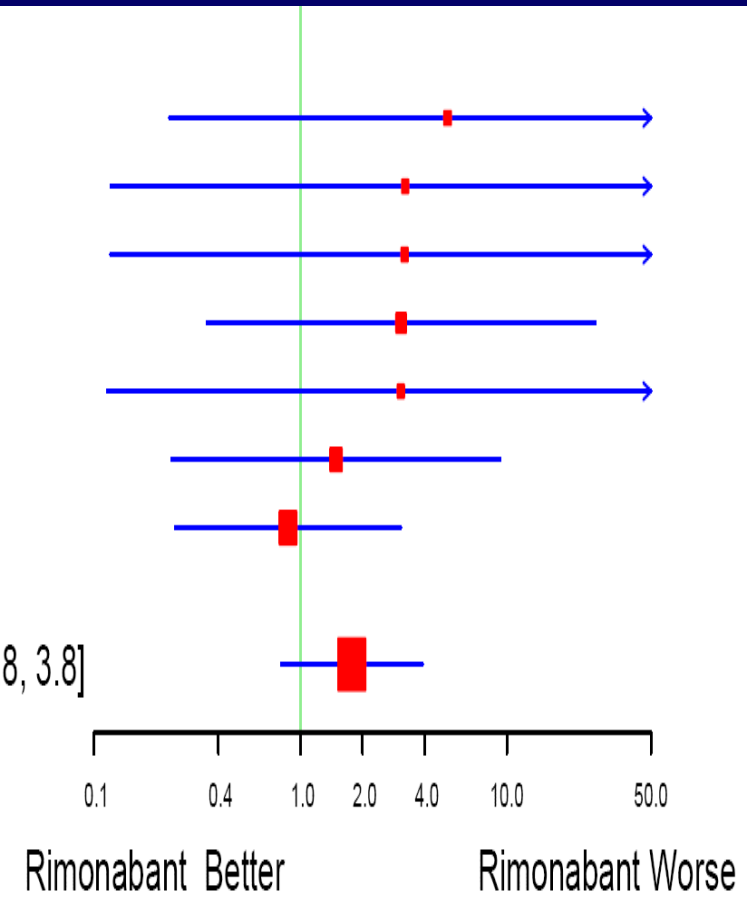
Odds Ratio of Suicidality All Studies

Population	Study #	20 mg n/N (%)	Plb n/N (%)	OR
OBE(DIA)	EFC4736	2/339(0.59%)	0/348(0%)	5.2
OBE(Ph2)	DRI3388	1/69(1.45%)	0/73(0%)	3.2
OBE(CRA)	EFC5031	1/76(1.32%)	0/80(0%)	3.2
OBE(EUR)	EFC4733	6/599(1%)	1/305(0.33%)	3.1
OBE(DIA)	EFC5825	1/138(0.72%)	0/140(0%)	3.1
OBE(LIP)	EFC4735	3/346(0.87%)	2/342(0.58%)	1.5
OBE(N.A)	EFC4743	7/1219(0.57%)	4/607(0.66%)	0.9
SMOKING	EFC4796	12/3023(0.40%)	0/2016(0%)	16.7
SMOKING	EFC4474	2/267(0.75%)	1/260(0.38%)	2.0
SMOKING	EFC5794	1/262(0.38%)	1/268(0.37%)	1.0
SMOKING	EFC4964	0/261(0%)	1/261(0.38%)	0.3
ALCOHOL	ACT4855	3/131(2.29%)	3/127(2.36%)	1.0
SCHIZOPH	METATRI	7/72(9.72%)	7/98(7.14%)	1.4
OBE(BED)	ACT3801	0/143(0%)	0/146(0%)	NA
Overall Suicidality Summary				1.9 [1.1, 3.1]



Odds Ratio of Suicidality Obesity Studies

Population	Study #	20 mg n/N (%)	Plb n/N (%)	OR
OBE(DIA)	EFC4736	2/339(0.59%)	0/348(0%)	5.2
OBE(Ph2)	DRI3388	1/69(1.45%)	0/73(0%)	3.2
OBE(CRA)	EFC5031	1/76(1.32%)	0/80(0%)	3.2
OBE(EUR)	EFC4733	6/599(1%)	1/305(0.33%)	3.1
OBE(DIA)	EFC5825	1/138(0.72%)	0/140(0%)	3.1
OBE(LIP)	EFC4735	3/346(0.87%)	2/342(0.58%)	1.5
OBE(N.A)	EFC4743	7/1219(0.57%)	4/607(0.66%)	0.9
Obesity Suicidality Summary				1.8 [0.8, 3.8]



Completed Suicides

- Four completed suicides reported to date - 3 in entire rimonabant clinical trial database; 1 post-marketing
- All three in clinical trials have occurred in subjects taking rimonabant:
  - RIO North America: 63 year-old male on Rim 5 mg
  - STRADIVARIUS: 36 year-old male on Rim 20 mg
  - CRESCENDO: 77 year-old male on Rim 20 mg
- Post-marketing: 33 year-old male on Rim 20 mg

Rimonabant and Suicidality
What is the Nature of the Association?

- Bias
  - Ascertainment
- Confounding
  - Weight loss itself
    - "Semi-starvation neurosis"
- Chance
  - Can never exclude the possibility of chance
  - Replication of findings across 9 of 13 studies
- Causal
  - Biologically plausible
    - ECS and CB1 receptor functions in CNS
  - Increased incidence of depression in clinical trials
  - Suicidality is a symptom of depression

Ascertainment Bias

- Patients who report common drug-related adverse events may be questioned more about other adverse events compared with placebo patients
  - e.g., increased reporting of sexual dysfunction in depressed patients taking an antidepressant might lead to further questions about other adverse events and possibly increase the odds of reporting suicidal symptoms
- Most common adverse event in rimonabant-treated patients is nausea
- Would increased reporting of nausea in a population of non-depressed patients on rimonabant lead to increased reporting of suicidal symptoms?
  - Depressive and anxiety events were reported on average 2 months later than nausea events

Ascertainment Bias (cont'd)

- Increased contact of rimonabant-treated patients with investigators (for any reason) would provide more opportunity to voice suicidal symptoms compared with placebo-treated patients
  - The mean and median number of study visits were 11.6 and 15 respectively, for both the placebo and rimonabant groups
  - All datasets with unscheduled visits recorded were reviewed – no disproportionately between treatment groups in the number of unscheduled visits

Ascertainment Bias (cont'd)

- Would have to be operative in 9 of 13 studies and explain odds ratios varying in magnitude from 1.4 to 16.7
- Assumes an equal background rate of depression in placebo and rimonabant-treated subjects
  - Recall:
    - Depressed mood disorders: 9% for rimonabant subjects vs. 5% for placebo
    - Discontinuation due to depressive disorders: 4.2% for rimonabant vs. 1.9% for placebo
    - Required anti-depressant therapy: 5% for rimonabant vs. 3% for placebo
- Background rate should obscure differences over time

Rimonabant and Suicidality
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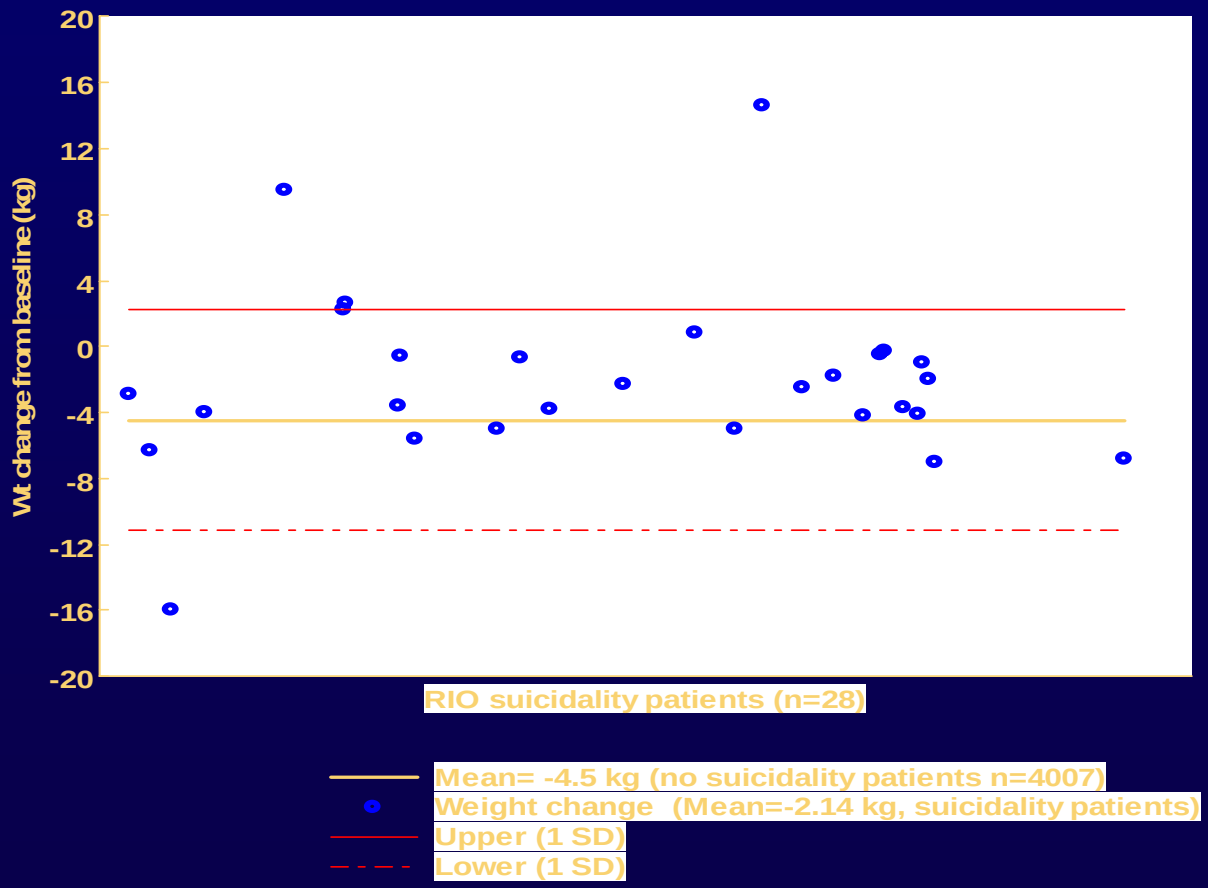
Suicidality and Weight Change



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  - Increased incidence of depression in clinical trials
  - Suicidality is a symptom of depression

Rimonabant and Suicidality Summary

- Meta-analysis indicates an increased risk for suicidality, specifically suicidal ideation, in subjects taking rimonabant 20 mg vs placebo
  - ↑ Relative risk ~ 80 to 100%
  - ↑ Absolute risk ~ 0.3%
  - NNH ~ 1 in 300 patients
- Estimates may be low given that:
  - Higher percentage of rimonabant patients dropped out of studies due to psychiatric adverse events

European Experience

- Rimonabant approved in 30 countries
- As of March 1, 2007, an estimated 100,000 people (mostly from the UK and Germany) have been prescribed rimonabant
- Top 10 Preferred Terms:
  - Depression
  - Nausea
  - Depressed mood
  - Anxiety
  - Fatigue
  - Dizziness
  - Sleep disorder
  - Suicidal ideation
  - Agitation
  - Asthenia

EMEA PostMarketing Data (Cumulative Since Approval)

Drug	# Psych AE cases	Total AE cases	Psych/ Total
Rim (2006)	208	384	54%
Sib (1999)	117	567	21%
Orl (1998)	208	2734	8%

EMEA PostMarketing Data (Cumulative Since Approval)

- Cases of suicidal ideation:
  - Orlistat (1998) 14 cases
  - Sibutramine (1999) 15 cases
  - Rimonabant (2006) 27 cases

Benefit vs. Harm

Potential Benefits

- Weight loss
- TG, HDL
- HbA_1C
- Fasting insulin
- Yet to be identified

Potential Harms

- Psychiatric
  - suicidality
  - depression
  - anxiety
- Neurological
  - dizziness
  - paresthesia/dysesthesia
  - tremor
  - seizure?
  - Nausea/vomiting
- Yet to be identified

CRESCENDO

- Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes
- 17,000 abdominally obese patients at risk for cardiovascular disease
- Rimonabant 20 mg vs. placebo
- ~ 5 years in duration
- Primary outcome: myocardial infarction, stroke, or cardiovascular death
- To be completed in 2010

Acknowledgements

Medical Review Team
Eric Colman, M.D.
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Karen Davis-Bruno, Ph.D.

Statistical Review Team
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J. Todd Sahlroot, Ph.D.

Project Manager
Patricia Madara

Questions for the Advisory Committee

1. Please discuss your level of concern regarding rimonabant and psychiatric adverse events, in particular depression and suicidality, and neurological adverse events, in particular seizures, and the reasons behind your thinking on these issues.

2a. Do you believe that the currently available data sufficiently characterize rimonabant's safety profile (vote requested)?

2b. If no, please discuss what additional data should be obtained.

Questions for the Advisory Committee

3a. Based on the currently available data, do you believe rimonabant has a favorable risk-benefit profile and should be approved for the indication of weight management in individuals with a body mass index of $\geq$ 30 kg/m^2 and > 27 kg/m^2 when accompanied by at least one comorbid condition (vote requested)?

3b. If no, please explain why and discuss what additional information the sponsor could obtain that might improve rimonabant's risk-benefit profile.